Published in final edited form as:
Curr Biol. 2013 January 21; 23(2): R79–R93. doi:10.1016/j.cub.2012.11.055.

The Biology of Fear

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Abstract

Each of us has felt afraid, and we can all recognize fear in many animal species. Yet there is no consensus in the scientific study of fear. Some argue that "fear" is a psychological construct rather than discoverable through scientific investigation. Others argue that the term "fear" cannot properly be applied to animals because we cannot know whether they feel afraid. Studies in rodents show that there are highly specific brain circuits for fear, whereas findings from human neuroimaging seem to make the opposite claim. Here I review the field and urge three approaches that could reconcile the debates. For one, we need a broadly comparative approach that would identify core components of fear conserved across phylogeny. This also pushes us towards the second point of emphasis: an ecological theory of fear that is essentially functional. Finally, we should aim even to incorporate the conscious experience of being afraid, reinvigorating the study of feelings across species.

Introduction

Could you be in a state of fear without feeling afraid? Is fear applicable to species like rats? What about flies? And how would you know?

Laypeople have no difficulty using the word "fear" in everyday conversation, yet are quickly stumped by questions such as these. So are psychologists and biologists. Despite an explosion of recent findings, spurred in large part by funding to help understand mood and anxiety disorders, the field of emotion research is more fragmented than ever. Much of this fragmentation, and much of the excitement, comes from the highly interdisciplinary nature of how fear is being investigated. A flurry of neurobiological data has come from two technical developments: fMRI (applied to humans) and optogenetics (applied to mice). Yet findings from these two approaches, together with ecological and psychological work, have not resulted in the emergence of any consensus on how to operationalize or investigate the emotion fear. Here I review this field from a broad perspective and suggest an approach to investigating fear that aims to move beyond the debates, and to reinvigorate studies by returning to some of the historical roots.

At the outset, we need an operational definition of "fear". The approach I advocate is pragmatic: fear is an intervening variable between sets of context-dependent stimuli and suites of behavioral response. Its usefulness is explanatory, and one can be agnostic about any correspondence with other psychological, let alone neurobiological, states. Such a variable could take on a consistent set of values within an individual, and differ

systematically between individuals, making it a candidate for a personality trait. It could be linked to variation in genotype, at least in part, making it a candidate for an endophenotype.

Several features of such a concept of "fear" are important to stress. First and foremost, it is a functional definition: fear is a central state of an organism (Box 1). It is not identified with the conscious feeling of being afraid, nor with fear behaviors such as screaming and running away. Both feelings and behavior can of course be used as evidence for a central state of fear, but the evidence for the state is not the state itself. Instead, fear as a central state is what causes the conscious experience (in some species and under some conditions) and what causes the fear behaviors (again, the details depending to some extent on species and circumstances). Fear in turn is caused by particular sets of stimuli (in a context-dependent way). Fear is what links sets of stimuli to patterns of behaviors. Unlike with reflexes, this link in the case of an emotion like fear is much more flexible (hence all the parenthetical qualifiers in this paragraph) and the state can exist prior to and after the eliciting stimuli (decoupling the state of fear from the eliciting stimuli, unlike with reflexes).

Specifying the sets of stimuli that normally elicit fear, and the sets of behavioral, autonomic, endocrine, and cognitive responses caused by fear, is of course a large and complex task. It is made easier by statistical regularities in the environment, and by phylogenetic continuity. There are evolved sets of behavioral packages to particular classes of stimuli encountered in a particular context in the case of rats [1], as in humans [2] (see also Table 3). Ecologists uncover the packages of behaviors and classes of stimuli as they occur in their natural environment, psychologists attempt to link their processing to the rest of cognition, and neuroscientists work on figuring out how the stimuli can be linked to the behaviors by the brain.

Historical and Current Debates

Theories of emotion have a long and checkered history, and perennial questions remain. How many emotions are there? What defines an emotion? Are emotions discrete or dimensional? What is their function? Which are unique to humans? Historically, much of the work has been done in philosophy and psychology with an almost exclusive focus on humans. There is debate concerning whether there is a small set of "basic" emotions that might be universal [3], and alternative accounts have proposed underlying dimensional frameworks and theories based on the psychological construction of emotions [4–6] (Table 1).

More recently, these debates have been informed by functional neuroimaging, and in particular by several meta-analyses that have tried to glean patterns of regional brain activation seen across larger numbers of studies. More than a century ago, the psychologist William James already envisioned emotions as corresponding to specific psychophysiological patterns in the body [7], although he recognized that each instance of an emotion might have a different pattern. Indeed, finding reliable psychophysiological patterns that would classify emotion categories (e.g., happiness vs. sadness) is an idea for which there has been little empirical support. Nowadays this picture has been transposed into the brain, and the debate remains alive: are there specific brain systems for happiness, for fear, for anger, for sadness? These emotions and others like them all seem distinct in terms of how we experience them, so one naturally wonders whether there are correspondingly distinct neural systems that generate them. Yet whereas some meta-analyses have found distinct patterns of brain activation corresponding to different basic emotions [8, 9], others have claimed that simpler or more abstract dimensional frameworks provide a better description of the data, or that the emotions we normally categorize simply do not have corresponding distinct patterns of activation in the brain at all [10, 11] (Figure

1). These neurobiological results, together with psychological studies, have kept alive arguments about whether there are basic emotions like fear, whether there are basic emotions but they are more general or abstract than “fear” [12, 13], or whether emotions such as fear instead correspond to regions in a broad dimensional space of valence and arousal, or of reward and punishment [4, 14–16], and might be to a large degree social constructs in humans [6].

All of this would have seemed rather bizarre to Charles Darwin [17], were he alive to witness these debates. Aside from utilizing mostly data from fMRI, the debate has also mostly used data from humans. Yet one of the key points Darwin made regarding emotions was their phylogenetic continuity: nonhuman primates, rodents, and even invertebrates, show strong homologues or analogues of several human emotions, both functionally and behaviorally (perhaps most clearly for aggression, fear, and disgust). Of course, there are aspects of all emotions that are likely unique to humans (e.g., those aspects dependent on language); and there well may be varieties of emotions unique to humans (e.g., emotions such as guilt or awe, although precursors to such emotions can likely be found in other animals as well). But it would seem that a logical starting point would be to pick an emotion for which there is good reason to believe in a strong phylogenetic continuity, understand its neurobiological basis in animal models, and then build on that core emotion scaffold the elaborations that the human brain provides [18]. There would be no better place to start such an endeavor than the emotion of fear.

Types of Fear

Some psychological theories propose that fear is a biologically basic emotion of all humans and many other animals [3], a view in line with most lay opinions as well. But several proposals beg to differ, arguing that emotions like fear should be replaced by a distinction between a fear and a panic system [12], or “survival circuits” related more broadly to adaptive behavior [13], or dimensional accounts such as reward and punishment [15]. A variety of evidence supports a view also in line with common usage: there are types fear.

The most common distinction is between fear and anxiety. Whereas fear is usually conceptualized as an adaptive but phasic (transient) state elicited through confrontation with a threatening stimulus, anxiety is a more tonic state related to prediction and preparedness--the distinction is similar to the one between emotions versus moods. Some schemes have related fear and anxiety to dissociable neural structures for mediating their behavioral effects, for instance the central nucleus of the amygdala (for fear), and the nearby bed nucleus of the striaterminalis (for anxiety) [19]. However, the dense interconnectivity of these two structures makes it difficult to uniquely assign either of them to participation in only one of these processes. A yet finer-grained classification makes distinctions between anxiety, fear, and panic, three varieties of fear that each are associated with particular packages of adaptive responses yet can all be mapped also onto a continuum of threat imminence (respectively, from more distal to more proximal [20]).

There is also evidence for multiple fear circuits in relation to the content of the threat. For instance, it has been argued that there are separate neural systems for fear of pain, predators, and aggressive conspecifics [21]. Each of these can be processed through a distinct sensory channel (e.g., somatosensory, olfactory, visual), engage distinct subnuclei in the amygdala and hypothalamus, and result in distinct responses mediated by particular parts of the periaqueductal gray (PAG) (respectively, ventrolateral, dorsolateral, and dorsomedial). Some of these distinctions among putative fear-subsystems are also supported by distinct molecular markers. For example, the predator-related subsystem is marked by the expression of steroidogenic factor 1 across several species, and corticotropin releasing factor is

expressed across a wide range of species and serves as a marker of the central amygdala in rodents (see Box 1 in [21]). A recent comparison between humans and mice revealed that copy number variations at specific genetic loci can influence remarkably specific types of fear: duplications of the GTF2I gene are associated with increased separation anxiety in both species [22].

Are these findings of multiple fear systems a problem for a concept of “fear” as a central state? Of course, partly different sets of individual neurons will no doubt be involved in processing different fear stimuli, or for that matter even the identical fear stimulus but on different occasions. This no more shows that there are distinct fear systems than does the fact that different visual images evoke somewhat different patterns of neural response in visual parts of the brain: nobody would conclude from this that there are many different visual systems. To demonstrate distinct fear systems, we would need to be able reliably to trace processing streams, and we would need to decide on the level of grain at which such processing streams are implemented in the brain. If we do find more than one such parallel processing stream for fear, then this could show that there are neurobiologically distinct types of fear that all share a common ecological theme (they are about threat, but different types of threat). But unless the number of such parallel systems gets very large, this would seem like progress in understanding the microstructure of fear, rather than an obstacle to using the term. In this respect, the data so far would seem to indicate that “fear” is quite a cohesive concept with likely fewer subtypes than, say, “memory”.

Three Recommendations for the Study of Fear

A functional definition of fear motivates three recommendations that form recurring themes throughout this review. One is that an investigation, and ultimate functional and neurobiological understanding, of fear requires a comparative approach: it cannot be investigated in humans alone. A second, complementary, idea is that understanding fear requires careful ecological work by biologists observing particular species in their natural environment in order to describe its functional role. This in turn suggests a need for close collaboration between psychologists and neuroscientists working in the lab, on the one hand, and biologists in the field, on the other. A third, more speculative, idea is that a fruitful purchase on understanding fear may be to investigate how it is experienced (felt) across species.

The first two recommendations capitalize on Darwin’s original insight about the phylogenetic continuity of emotional expressions [17] and assume that it will be easier in many respects to understand fear in rodents, zebrafish, or even invertebrates, than in humans. A benefit of including animals with simpler brains in this range is that it forces us towards a concept of a fear state that is more abstract and functional, rather than one tied to any particular neurobiological implementation or type of conscious experience. Another reason it is advantageous to investigate fear in nonhuman animals is of course that many experiments are simply much easier, or only feasible, carried out this way-- ranging from optogenetic manipulation of precisely defined cell populations, to mapping of gene loci that contribute to fearfulness. Inducing fear in the laboratory in ecologically valid ways also is much simpler in animals other than humans (who typically know they are part of an experiment).

The third recommendation opens the door for a particularly exciting set of future studies. It not only investigates what the layperson might consider the most important and salient aspect of fear (how it feels), but also may provide a clever experimental approach for how to classify the multi-dimensional behavioral and cognitive accompaniments of fear. The basic idea is that the brains of higher mammals (and perhaps other animals) already do a lot of the

work for us: they already represent emotional states so as to provide the animal with a more compact description of its current functional state. Rather than attempting to record and extract patterns for “fear” from all the varied somatic, visceral, endocrine and cognitive changes that can accompany an emotion, we might simply look to the interoceptive self-representations in the brain that map these variables [23, 24]. In humans, their joint representation provides an important part of the information on the basis of which people can verbally report that they feel afraid. Of course, there are well-known difficulties with using verbal report as the sole source of data; the recommendation here is not to rely on verbal report per se, but to push it back one level to measurement of the neural representation on which verbal reports are in part based (a measurement that is of course also available in nonverbal animals, once we know where to look). This third theme goes hand in hand with current developments in the neurobiology of consciousness, and it may bring back to the scientific study of emotions a topic that, ever since Behaviorism, has been excluded (despite the fact that many modern neurobiological views on emotion now mention it [12, 13, 15, 24, 25]).

Neural Circuits for Fear

Many cortical regions together with midbrain and brainstem nuclei participate in fear responses, but how they all interact still remains relatively unclear (see [12, 26, 27] and Figure 5 for some partial schemes). I do not attempt any kind of comprehensive review of the neurobiological literature here, but outline some of the best studied circuits. It is important to reiterate that the neurobiology of fear is still in its infancy; there are many structures that likely play key roles, but about which we know very little. For instance, subdivisions of the habenula likely contribute to signaling fear-related information to brainstem nuclei, and provide signals about punishment or absence of reward to reward-learning systems [28]; parts of this pathway are highly conserved across vertebrates [29]. Stress and anxiety have also been reported to activate the lateral septum [30], although the precise and causal role of this structure remains rather unclear. None of these structures is commonly encountered in neurobiological studies of fear in humans.

Of course, the functional role of the participating brain structures depends on specific neurotransmitters and their receptors. This level of explanation has been informed by the actions of specific drugs, such as the anxiolytic effects of benzodiazepines. Of some interest have been drugs acting on serotonin reuptake transporters, a very widely prescribed class of agents for treating mood and anxiety disorders (such as the drug Prozac). There is some support for a classic theory of the differential actions of serotonin in facilitating anxiety but inhibiting panic [31]. Similar attention has also been devoted to another neuromodulator controlled by specific brainstem neurons: norepinephrine. A distinguishing feature of both the serotonergic and noradrenergic systems is that a relatively discrete population of neurons (in the dorsal raphe, and the locus ceruleus, respectively) innervates a wide swath of distal targets, making possible precisely the kind of global and coordinated effects on information processing that an emotional state like fear requires.

Perhaps the best understood axis of processing fear in the mammalian brain involves structures connected with the amygdala (Figures 2,5). At the cortical end, the most prominent of these is the orbital and medial prefrontal cortex, including cingulate cortex. At the other end are the hypothalamus, periaqueductal gray (PAG), and many brainstem nuclei as well as the intermediolateral cell column of the spinal cord and peripheral components of the autonomic nervous system. It is tempting to view the function of this assembly of structures in terms of the lower levels implementing emotional responses, and the cortical levels exerting modulatory control and regulation (see below). While such a view is not entirely inaccurate, it fails to capture the complexity of how these different structures

implement fear -- in good part due to massive reciprocal interactions between all the components. For instance, the amygdala projects to the PAG and conversely. The amygdala is also reciprocally connected with prefrontal cortex, and concurrent recordings in both structures clearly show that there is no simple serial processing but a much more complex iterative flow of information [32]. Two other sets of structures that need to be incorporated into the scheme are parts of the basal ganglia involved in reward processing and instrumental behavior, and the insula, involved in interoception.

Fear and the Amygdala

The basolateral amygdala receives most of the sensory inputs that specify fear associations (with the exception of olfactory input, which comes into the medial nucleus) and selective optogenetic activation of neurons within this nucleus is sufficient to associate the incoming sensory information with unconditioned fear responses [33] (Figure 2). The central nucleus of the amygdala is widely considered the main output regulator for mediating fear responses, and these are in turn mediated by distinct subdivisions of the central nucleus. Whereas some of these neurons can inhibit cholinergic targets mediating cortical arousal (in the substantiainnominata, diagonal band of Broca, nucleus basalis), they can at the same time promote freezing through projections to the periaqueductal gray [34]. The flexible modulation of different downstream fear components by the central amygdala depends on an intricate inhibitory control balance internal to the amygdala [35, 36].

Studies of the amygdala in humans have implicated this structure in the recognition [37], expression [38], and experience [39] of fear. However, in human neuroimaging studies it is activated not only in anxiety and phobia [40] but by a broad range of unpleasant or pleasant stimuli [41–43], including highly arousing appetitive stimuli such as sexual stimuli or one's favorite music [44, 45]. The enormous range of stimulus properties that have been reported to activate the amygdala has given way to views that try to provide a more unified picture. Such accounts typically acknowledge that the amygdala plays an important role in fear, but stop short of endorsing the claim that this is a basic function. Instead, they propose that it is merely one example of a broader and more abstract function, such as processing arousal, value, preference, relevance, impact, vigilance, surprise, unsigned prediction error, associability, ambiguity or unpredictability. The extent to which any of these functions are domain-specific (notably, in regard to processing social stimuli) remains an open question [46].

Much of this literature has interacted with the amygdala's well-known role in memory [47] and attention [48], with the emerging possibility that the amygdala may play a more modulatory [49], developmental [50], and learning-related role [51], rather than a principal role in the on-line processing of fear. Somewhat relatedly, there has been a shift towards more network-based views of fear processing, in which structures such as the amygdala are nodes in an anatomically much more extended collection of structures [52]. This shift emphasizes the fact that the initial question was simply ill-posed: "what does the amygdala do?" is not a sensical query in the first place, because the amygdala in isolation does nothing; it all depends on the particular network in which it participates. This also points us towards a different view on the search for neuroimaging activation patterns specific to certain emotions: the circuits responsible may simply be too distributed to resolve using techniques such as fMRI.

As important as moving from the amygdala outwards to include it in larger networks is moving inwards to consider its internal components. Earlier work in rodents began to show that different amygdala nuclei are involved in different types of fear-related behaviors, such as innate responses to conditioned stimuli or actions to avoid them (e.g., [53, 54]). However,

whereas the earlier studies investigated these issues using bulk lesions of tissue (and generated some conflicting findings), it is now clear that the level of resolution required is at the level of specific neuronal subpopulations, often intermingled even within a single nucleus. Such subpopulations are distinguishable by a number of criteria, including the set of genes they express, their morphology, and most importantly their connectivity and electrophysiological properties whereby they subserve particular functions in processing fear. Current investigations of this issue use optogenetics to address this issue. In this technique, light-activated ion channels are expressed in specific neuronal subpopulations through their coupling to a promotor specific to that subtype (alternatively, one can also engineer ion channels gated by exogenous drugs that can then be administered experimentally). This is achieved best in transgenic mice, although it also possible to do it through focal injection of viruses, opening the door to such manipulations in monkeys as well. Optogenetic studies have demonstrated a tightly regulated network of inhibitory interneurons within the central nucleus that controls how sensory input (coming into the basolateral amygdala) can influence outputs to structures such as the hypothalamus and periaqueductal gray (e.g., [35, 36]). This level of grain is impossible to investigate in humans so far, and poses a major challenge for how to interpret results from functional neuroimaging studies, which pool changes in blood-oxygenation-related activation over voxels several millimeters in size (typically, 15–20 cubic millimeters) over a timecourse of a few seconds.

As with midbrain and brainstem structures, the amygdala's role in fear processing is highly conserved across species ranging from humans [55], to monkeys [56, 57], rodents [58, 59], and even reptiles [60], mirroring its conserved pattern of connectivity [61]. Sorely needed are systematic comparative studies that focus on specific structures and networks, and that map out the similarities and differences in functional components. For instance, the role of the amygdala in associative learning of fear appears to be ubiquitous across species; the set of unconditioned stimuli that it processes vary to some extent; and its role in the conscious experience of fear has been investigated only in humans [39].

Is Fear Adaptive?

Fear is commonly thought to have adaptive functions in terms of both cognition and behavioral response. Unlike reflexes and fixed-action patterns, the relationship between stimuli and behaviors mediated by fear is highly flexible and context-dependent (see "modulation of fear", below). Indeed, this flexibility is part of what distinguishes emotions: they are "decoupled reflexes", central states more akin to personality traits and dispositions. One feature that highlights this are the highly diverse yet integrated sets of psychophysiological, cognitive and behavioral changes that all serve as indices of a central state of fear (Figure 3).

Yet one of the most prominent behavioral aspects of fear in humans remains of debated functional significance: facial expressions of fear. There is a vast literature regarding emotional facial expressions (probably the single most commonly used class of stimulus in human studies of emotion), with strong claims regarding their cultural universality or relativity, their biological primacy or social construction. But Darwin himself pointed out that emotional expressions could very well have evolved without having adaptive functions: they were, to use his phrase, "serviceable associated habits", vestiges of behaviors that were once adaptive [17]. This claim is only partly true, however: it might pertain to such behaviors as emotional facial expressions, body postures, and alarm calls, but not to all fear behavior. And even these aspects of fear behavior are certainly adaptive. Their main functions have simply changed, and now they play a primary role in social communication rather than direct protection and defense [62–64]. There also are still residual adaptive

functions of many of these expressive behaviors, which give us some insight into how they likely evolved. For instance, the wide eyes and flared nostrils typically associated with facial expressions of fear not only communicate fear to other viewers, but in fact alter sensory perception by increasing the eccentricity in the visual field of stimuli that can be detected, and increasing airflow through the nose so as to better detect olfactory cues [65].

The Modulation of Fear

A key current challenge is to assemble our knowledge at the level of individual structures, nuclei, and neuronal populations, to knowledge at the level of distributed large-scale networks (a challenge that pervades all of emotional and social neuroscience [66]). An emerging theme from such network concepts is that there are structures more concerned with directly orchestrating fear-related responses (e.g., PAG and hypothalamus), and structures more concerned with context-dependent modulation. Of particular interest for the latter have been prefrontal cortices, which some schemes have partitioned into orbital and medial networks, subserving processing of emotionally salient sensory stimuli and orchestrating of visceral emotional responses, respectively [67]; and into ventromedial and dorsolateral networks related to reward processing and cognitive control [68]. Moreover, such networks can be related to specific neurotransmitters and levels of action for pharmacological intervention [69]. The amygdala plays a key role in mediating between brainstem and cortical levels, with specific nuclei participating in distinct networks that may be similar across species [61]. Dissecting these networks and understanding their pharmacology, constitutes one of the main research components towards treating phobias and anxiety disorders [70].

The context-dependency of fear is seen in terms of the eliciting circumstances (e.g., flight available or not, which will elicit escape vs. freezing; Figure 4a), type of threat (predator, conspecific, unknown), distance to the threat (and hence time; i.e., predatory imminence [20]), and time elapsed since a threat was encountered (resulting, in order, in behaviors such as active defense and flight, risk assessment, inhibition of movement, distancing). All of these have been described in some detail by ethologists working on fear in nonhuman animals [71, 72], and emphasize the temporally extended and dynamic nature of a fear state that we noted earlier. There are many examples that networks within the medial prefrontal cortex play a key role in the modulation of fear-related processing, by projecting to targets such as the amygdala, hypothalamus, and brainstem. For instance, prefrontal regions are implicated in the extinction of conditioned fear responses, and lesions to ventromedial sectors of the prefrontal cortex in humans may actually exert a protective role in the acquisition of disorders such as post-traumatic stress disorder [73].

Another example implicating the prefrontal cortex comes from studies of threat imminence: proximal predator threats require immediate flight; anticipations of dangerous future situations require long-term planning and control [20, 74] (cf. below). These distinctions are mirrored in the neural structures that have been emphasized: brainstem and midbrain structures on the one hand, and forebrain, in particular prefrontal cortex, on the other [27, 58]. Yet a strict dichotomy is probably inaccurate, and a better model may be to think of all “lower” structures as involved in both immediate and delayed responses, with the latter including more forebrain modulation; it has also become apparent that loops involving forebrain processing can be remarkably rapid [75].

An interesting line of work that ties together the themes of specific neurotransmitters (serotonin), prefrontal networks, and particular subtypes of fear comes from analyses of an animal’s control over a stressor. Uncontrollable stress has long been known to lead to more severe health consequences, and to specific behavioral adaptations such as “learned

helplessness". This behavior depends in part on serotonergic modulation via the dorsal raphe nucleus, but also requires input to the dorsal raphe from the ventromedial prefrontal cortex to signal that a stressor is uncontrollable [76].

Responses and Stimuli Associated with Fear

There are many behavioral fear responses that can be used by conspecific observers to infer fear, and several of them have been quantified as behavioral markers of fear by human investigators (cf. Table 2 for a partial list). These include such laboratory measures as freezing (immobility), increased startle, and increased heart rate. More species-specific are alarm calls signaling danger, which are observed in species from monkeys [77] to rats [78] to birds [79]. Humans are relatively unique in their repertoire of emotional facial expressions (although chimpanzees, but not monkeys, can make such expressions as well, even though we generally do not know what they mean). In addition to behavioral responses and autonomic changes, there are effects of fear on nearly all aspects of cognition, ranging from attention to memory to judgment and decision-making (Figure 3b). Recent emphasis on the adaptive nature of emotions has studied how emotional states can influence decision-making, in particular an animal's bias towards uncertainty and risk [80]. Systematic effects of putative fear states on choice behavior have been claimed even in bees [81].

Similarly, we can think of several broad classes of prototypical fear-inducing stimuli [82]. There are those stimuli whose detection parameters have been set by evolution, for instance visual presentation of snakes or spiders in humans [83], or the odor of a fox for a ground squirrel. The bed nucleus of the striaterminalis has been implicated in unconditioned fear responses (freezing behavior) to a specific odor component of fox feces, trimethylthiazoline [84]. Then there are those stimuli that an organism has learned are dangerous through experience (or, in some species, social observation), as well as those stimuli that are not themselves dangerous but have been associated with the above two classes of stimuli and can thus serve as conditioned warning cues. It is for the first class of stimuli mentioned above that there are the strongest arguments for "modules" for fear processing: relatively encapsulated processing streams that are triggered rather rigidly by specific stimuli, over which we have little control, and that depend on some specialized neural structures [21, 83]. However, most stimuli of which humans are afraid are probably learned socially [85], a mechanism also ubiquitous in other animals [86]. Learning about a harmful stimulus from another animal involves the amygdala, in both rats [87] and humans [88].

An interesting aspect of fear-associated behaviors are those actions taken not proactively but in order to terminate the state of fear itself: just as the anticipation of fear motivates behavior, so too does anticipation of its end. Cues associated with the cessation of fear can reinforce certain behaviors [89], suggesting a broader perspective in how fear behaviors unfold in time. Rather than thinking of a fear state as a static functional state, or as a fixed sequence triggered by a fear-inducing stimulus, we should conceive of it as a dynamic process. The duration of this process would extend from the cues that initiate it through to the stimuli encountered as it unfolds, the animal's response, and its own perception of the interaction between the two, to the final reestablishment of homeostasis. While this makes things more complicated, it also imposes bounds, since specific structures come into play at certain points in time.

Distance and Intensity

One of the most prototypical of threat stimuli is an approaching predator (Figure 4). This is a good example for the functionally specific organization of fear behaviors: animals typically respond with several distinct packages of adaptive behavior, depending on the distance. These range from freezing (to avoid being detected) to vocalization (to warn others or

recruit help), to defensive attack. Such behaviors also show substantial differences between individuals and species: domestic as well as lab-reared wild rats tend to switch from freezing to escape when an experimenter is around 1–1.5 meters away, whereas wild trapped rats do so already at a mean distance of 2.5m [90].

A related stimulus attribute is intensity. Sudden-onset, or high intensity physical properties of stimuli in many cases elicit fear. To some extent, this can simply reflect the graded quality of fear cues, and of course intensity is often correlated with distance. Shrinking interpersonal distance and increasing sound intensity are two examples; in these cases both are known to activate the amygdala [91, 92]. It has been known for some time that the different packages of fear behaviors that can be engaged at different distances or intensities (e.g., freezing versus fleeing) also engage different sets of neural structures [93], the details of which are now being uncovered. Columnar arrangements of neurons within the periaqueductal gray play an important role in these different components of fear responses, with more dorsal regions controlling active escape behaviors, and more ventral regions controlling inhibition (e.g., freezing) [94]. However, as we noted earlier, there are substantial ascending projections from the PAG as well, making the functional role of this brain region considerably more complex than a mere orchestration of emotion-related output.

Switches from passive to active fear responses (freezing to fleeing) are tightly dependent on distance from a predator [20, 27], since different behaviors would be adaptive at different distances (e.g., possibility of evading detection versus need to engage). Neural correlates of such shifts have been observed in relation to several structures in addition to the PAG. The central nucleus of the amygdala can orchestrate switches between forebrain arousal and freezing in mice [34], and shifts from activation in the prefrontal cortex (distal threat) to PAG (proximal threat) have even been observed in human neuroimaging studies [95]. A related finding showed that activation in the bed nucleus of the striaterminalis correlated not with the sheer physical distance of threat (in that study, a tarantula), but with whether it was approaching or receding [96] (Figure 4). Flexibility and learning in the elicitation of fear depends on plasticity and inhibitory control within the amygdala [35] as well as both ascending (e.g., from the PAG) and descending (e.g., from the prefrontal cortex) modulation. Exactly how an organism integrates sensory information together with its own coping ability in order to make the choice to switch from freezing to fleeing is a very rich question in the ecology of decision-making that deserves more study across species.

A major contextual factor in the evaluation of fear-inducing stimuli is whether or not escape might be possible, or whether the threat seems inescapable, a distinction related to the modulatory factor of control that we noted earlier. The former is typically associated with flight, whereas the latter is typically associated with freezing and defense (Figure 4a). This dimension can require substantial evaluation and amounts to ongoing monitoring and decision-making. The availability or unavailability of a place for concealment or escape has also been found to modulate the scenario-elicited fear behaviors of humans, in general quite in line with what would be predicted based on observations in rodents [2] (cf. Table 3). In broad terms, this category is related to an animal's model of its ability to cope with a threat, an ingredient that has long been highlighted in human psychology by appraisal theories of emotion [97].

Other Stimulus Attributes

Another quite broad stimulus attribute that elicits fear is unpredictability. This can be a computationally more complex cue to detect, since it depends on comparisons of stimuli, or patterns of stimuli, over time. Several commonly used laboratory assays for fear, such as

open-field tests, neophobia, and measures of latency to emerge from a secure nest, likely tap this category as well (cf. Table 2); the fear-related behaviors elicited are the complement of exploration. These fear-inducing attributes are found from mammals through zebrafish [98].

There are various types of unpredictability: temporal uncertainty in the occurrence of a stimulus, novelty of the stimulus itself, and even the context of knowing that one does not know much about a given stimulus [99]. One can identify at least two ways in which the occurrence of a stimulus is uncertain: there is a known probability (<1) associated with its presentation, an attribute economists refer to as “risk”, or there is uncertainty even about this probability (one does not know how risky it is), referred to as “ambiguity”. All of these aspects of unpredictability have been shown to activate the amygdala [100, 101], and typically include a constellation of behaviors referred to as “risk assessment” that involve cautious sampling of the environment in order to obtain more information and reduce unpredictability.

An important category of fear-inducing stimuli are social. Animals can show strong fear behaviors in response to aggressive or dominant conspecifics. One common model of mood disorders in rodents is social defeat, a set of long-lasting submission-related behaviors induced by the inability to defend cage territory against the intrusion of an aggressive and dominant male. This social stimulus reliably elicits neuronal, endocrine, and immune changes indicative of anxiety, although longer-term effects are more akin to phenomena such as learned helplessness and depression [102]. Similar types of responses are found in other species ranging from zebrafish to humans. A specific category of fear arises when infant mammals are separated from their mother, a form of immediate separation anxiety connected with high-frequency (in many mammals, ultrasonic) distress vocalizations of the young; some theories have termed this type of fear “panic” to distinguish this system from other fear systems [12] (see also Box 3) and it can be modulated by specific genes as noted earlier [22]. In humans, social aspects of fear can be elicited by cues such as untrustworthy faces or invasion of personal space, all stimuli that reliably involve the amygdala [91, 103, 104].

Animals can also show fear in response to subtle cues picked up from the fear induced in another conspecific; these can be innate (e.g., chicks respond to alarm calls), an example of social learning (e.g., infant monkeys can learn from fear behaviors of adults [105]), or involve unknown social signals (e.g., rats placed in contact with other rats who experienced electric shock show amygdala activation [87]). Somewhat the flip side of increasing sound intensity that we noted above, sudden cessation of background sounds can be a social signal of fear in rodents as well [106]. In zebrafish, injured fish release a chemical that functions as an alarm signal: when detected by other fish, it causes a graded increase in fast swimming behavior [107]. Social communication of fear is even seen in crickets (in response to spiders) [108]. Another good example from invertebrates is the emission of carbon dioxide by *Drosophila* when flies encounter an innate fear-evoking stimulus such as electric shock. This odor can evoke avoidance behaviors in other flies, thus serving as a social signal, and is processed by a highly specific neural circuit [109]. A class of social stimuli that commonly induces anxiety and is likely unique to humans is public evaluation, such as when one is forced to give a public speech; this potent scenario is in fact used experimentally to induce anxiety (e.g., the Trier Social Stress Test).

One intriguing class of stimuli that can trigger states of panic are interoceptive signals. In particular, signals related to suffocation and panting are known to be represented in the periaqueductal gray [110] and the amygdala. There is a specific pH-sensitive ion channel expressed on neurons within the amygdala that may directly sense acidosis due to rising carbon dioxide levels [111]. Other examples would include strong interoceptive signals of

major homeostatic imbalance, or organ failure (e.g., a heart attack, or a stroke). It remains relatively unclear to what extent direct interoceptive signals about such events can be used to trigger fear, and to what extent fear is instead triggered more derivatively by secondary consequences and background knowledge (at least in humans).

Finally, it is worth emphasizing that humans stand out from other animals in having fear and anxiety triggered not by occurrent stimuli, but merely by thinking about such stimuli. The bulk of psychopathology arises from worrying about what could happen and what might be, often to the point of distorting what actually is. This aspect of fear induction in humans probably also contributes to the impression we have that fear depends very much on conscious experience.

Conscious Experience of Fear

Clearly, different instances of fear and anxiety do all feel similar, and we categorize and verbally describe them as similar. This fact must be reflected both in psychology and neurobiology. At the psychological level, two sets of theories have attempted to incorporate the diversity of stimuli, situations, and behaviors related to fear, on the one hand, with their apparent psychological and subjective unity, on the other. The first such theory is appraisal theory, a theory about the adaptive functional role which fear is thought to accomplish. Older theories that had lists of functional evaluations [97] have been advanced with more recent accounts that relate specific stimulus evaluation checks to specific points in a processing sequence [112]. The second psychological theory is the conceptual act theory [6, 14, 113]. According to this constructivist framework, our experience of fear, and certainly our reports of having fear (and any other emotion), are a highly cognitive synthesis. The synthesis begins with an initial core affective state (that is perhaps no more finely differentiated than along dimensions of arousal and valence [4], two dimensions frequently thought to capture much of the variance across emotions [16]) and then incorporates not only interoceptive and somatic knowledge of the state of one’s body and of one’s actions, but also of the context-dependent situation, knowledge stored in memory, and much explicit information stored in language and acquired in a particular culture. Emotion categories such as fear are then seen as highly constructed, rather than as biological primitives (cf. Box 1). A major challenge for future work will be to elucidate the neural substrates of these psychological components, and to probe whether anything similar can be found perhaps in nonhuman primates or whether this aspect of fear is unique to humans.

While this review advocates a broadly comparative and functional approach to fear, there is no reason to exclude the conscious experience of fear. Instead, it seems timely to incorporate modern theories of consciousness into the study of emotion, including the study of fear in nonhuman and hence nonverbal animals [12, 114]. There are several advantages to doing so. First and foremost, it would seem compelling to try to incorporate what laypeople find the most salient component of a state of fear. We already know that healthy humans feel fear, that such feelings are the main basis for complaint in psychiatric anxiety disorders, and that they are abolished by lesions of the amygdala [39]. It is a perfectly respectable scientific question now to ask whether monkeys, rats, reptiles or flies have feelings of fear, although it requires some dissection of components of feeling fear (Box 2). Of course, we could not approach this question in the same way that we typically do in humans (by using language and asking). Instead, we would need to use other measures that all require some neurobiological theory of consciousness. But something like this has already been done for other types of conscious content: for instance, patients who cannot answer any questions, and who cannot respond behaviorally in any way, show brain activation in response to verbal instructions that is very similar to the activation seen in healthy, conscious people (in that study, instruction to imagine playing tennis activated brain regions normally associated

with such mental imagery, for instance [115]). This allowed the authors of that study to infer that the patients were conscious, in the absence of any behavioral measure. Extending such an approach to nonhuman species requires a broader theory of consciousness, but the basic idea is no different in principle. There are in fact several modern theories of consciousness that are functionally congenial to understanding the conscious experience of fear, and that offer testable neurobiological hypotheses.

Three such theories are focused, respectively, on the information-conveying nature of conscious experiences [116, 117] (integrated information theory), on their ubiquitous functional consequences [118] (global workspace theory), and on their subjectivity [23, 24, 119] (theories of subjectivity and the self). The reader is referred to the original references for further description of these theories, but each of them makes neurobiological predictions. Briefly, these theories could relate to our investigation of fear as follows.

The integrated information theory proposes that a specific conscious experience conveys a very high amount of information, since it is distinct from so many other experiences and yet typically integrates very many component attributes [116, 117]. Thus, all the different shades of feeling fear should correspond to informationally distinct, yet richly integrated, brain states at the neuronal level. This would put an upper bound on the number of distinct fear experiences (or emotion experiences more generally) that any organism could experience, deriving from the complexity of the neural systems instantiating fear. Presumably, the addition of further cortical territory into the representation of fear in humans allows for much more nuanced and elaborate experiences of fear [14]. There are some efforts underway to estimate integrated information in the brain (a very difficult problem) from measures such as EEG.

With respect to the second popular theory, global workspace theory, a conscious state of fear has access to a vast number of other cognitive and behavioral processes [118], with the result that fear modulates attention, memory, perception, and decision-making. The theory often appeals to nuclei in the thalamus that have the requisite wide connectivity, but the connectivity of the amygdala could also support such a network in the case of fear [48, 120], and may explain why focal lesions to this structure can abolish the ability to feel fear, at least in humans [39].

Finally, harking back to William James' original insight [7], the content of our conscious experience of fear includes interoceptive information about the state of our body and mind, and requires some degree of self-representation [23, 24, 119]. The subjectivity of feeling afraid requires not only a subject to experience the fear, but also to a good extent specifies why fear feels the way that it does, at the same time providing the organism with information about its homeostatic state, its state of preparedness to cope with an environmental challenge, and motivating it to engage in instrumental behavior. These components have been hypothesized to depend on regions of the brain that map interoceptive information, such as the insula and anterior cingulate cortex [23, 25]. This view also makes the strong prediction that species without interoception cannot feel fear -- a conjecture that remains entirely unexplored. One intriguing possibility is that a readout of the neuronal representation of fear in interoceptive structures such as the insula might in principle provide neuroscientists with the same information that it provides to the subject feeling fear. This could allow a direct link between psychological theories of emotion that place a premium on our experience of them, on the one hand, and neurobiological substrate, on the other. In a sense, it would resurrect William James' original idea, but use the brain's representation of the emotion itself rather than attempt to measure all the varied somatic correlates of the emotion.

Conclusions and Open Challenges

There is no single brain structure for processing fear, and even a small set of necessary and sufficient structures has not emerged. One likely reason that it has been difficult to find clear evidence of a dedicated fear circuit from fMRI studies in humans [10] is that it is now apparent that rather different emotional behaviors, ranging from defense to aggression to mating, are controlled by specific populations of neurons that are spatially within the same structure and hence unresolvable using fMRI (e.g., [35, 121, 122]). Much the same is true of value encoding in general: neurons within the amygdala encoding positive or negative reinforcement appear to be closely intermingled, making their visualization with typical fMRI approaches problematic [123]. Another reason is that fear evoked by different classes of stimuli (unpredictability, social, predators, etc.) may be processed by partly separable neural systems [21, 124]. There is better evidence, and more reason to believe *a priori*, that extended systems comprised of a network of structures could be identified. Some fMRI studies have suggested this, and several models have been proposed [12, 27]. Ultimately, we may need to redraw the boundaries of the component structures, however: networks for processing fear will consist of specific subpopulations of cells extended across an array of structures.

How is it that I can tell my cat is afraid? Typically, I figure this out from all evidence available, which includes the current situation (are there fear-inducing stimuli or context) and the animal's behavior. Darwin's detailed observation of emotional behaviors in babies, adult humans, dogs, cats, and other animals demonstrated that many behaviors were remarkably similar across species [125]. Of course, there are also differences between species, differences between individuals, and things are vastly more complex in humans than in a mouse. But comparative as well as developmental observations suggest that a fruitful starting point is to begin with a primitive concept of fear that is shared across mammals (or even more broadly than that), and then investigate the variations on this theme. The neurobiological evidence is then one additional piece of evidence, supplementing the behavioral and situational clues, and allowing us to begin constructing causal links between these.

In humans, there is of course another component of fear: its conscious experience. A complete program for the scientific study of fear will need to go hand-in-hand with the development of neurobiological and functional theories of conscious experience. The questions are extremely challenging to answer, but they are questions that make sense and are interesting to try to answer. At what level of phylogeny does the feeling of fear become incorporated into its neural representation? Why? (what happened in evolution to make it adaptive to have this added component?). What components of fear constitute the contents of its conscious experience? Do we have any control over which components of fear we can become aware of? (can we train ourselves to become more or less aware of feeling fear?)

Three prominent challenges for the future, then, map onto methods, cross-species comparisons, and investigation of the conscious experience of fear. The first will require the combination of single-neuron measurements and manipulations at the level of optogenetics with a much larger field-of-view (ultimately, a whole-brain field-of-view). The second will require funding and research consortia that investigate fear across a range of different species, paying close attention to ecologically validity, especially in experiments with humans. The third will require close interface with people working on consciousness, and more precise hypotheses regarding the neurobiology of consciousness. All three taken together may constitute the future science of fear.

Acknowledgments

I thank Michael Davis, Dean Mobbs, Adam Anderson, Lisa Barrett, Jaak Panksepp, Shuo Wang and Geoff North for providing many helpful comments and no consensus. I am especially indebted to David Anderson for comments and discussions that have considerably shaped the conceptual aspects of this review. Supported in part by grants from NIMH.

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Box 1. The functional state of fear

This review urges a functional concept of fear, defining this emotion in terms of being caused by particular patterns of threat-related stimuli, and in turn causing particular patterns of adaptive behaviors to avoid or cope with that threat. This immediately raises an important question: are we discovering “fear” through objective scientific investigation, or are we imputing it through our concept of “fear”? In the same way that studies in physics would not reveal to us a material object category such as “chairs”, neurobiological studies of fear might not carve out a state of “fear”. Instead, fear, like chairs, might be a psychologically constructed category (this of course ultimately makes it no less biological) [6]. The answer to this worry depends on assuming that patterns seen by scientists, in particular ethologists, are also patterns seen by evolution. Unlike distinguishing categories such as “table” and “chair”, which are also functional, but entirely socially constructed, categories such as “fear” and “disgust” correspond to functional categories that evolution has sculpted. Without this assumption of functional homology, it becomes impossible to study fear across species. This is also the reason why it would be nonsensical to assign “fear” (or any other emotion) to an alien species from another planet (unless we knew a lot about its environment and the mechanisms for evolution on that planet, and these were sufficiently similar to the case on earth).

Another question concerns how fear would relate to other central states, such as learning or attention. Just like a state of fear interfaces causally with stimuli and behavior, it is embedded in a network of causal relationships with other cognitive processes. Are these other processes partly constitutive of fear? A state of fear is typically constituted (in part) by motivating the organism to behave in a certain way, modulating memory, and directing our attention. So, those aspects of motivation, attention and memory, just like certain aspects of behavior, are part of an adaptive response to a threatening stimulus. As such, they are constitutive. However, whereas the causal links to stimuli and behavior are functionally definitional of fear, the links to other central states have a more empirical flavor to them: we need to do psychology and/or neuroscience to discover them, and we may not want to tie the state of fear too closely to their necessary causal interaction because not all animals may have the same psychological or neurobiological architecture.

The functional approach to defining fear as a central state evoked by threatening stimuli can be criticized as seemingly circular. What is fear? The state evoked by threat. What is threat? That which causes fear. The reason that our definition of fear is not circular is that it is anchored not only in stimuli, but in behaviors. Certain sets of stimuli and behaviors covary; if they did not, we would never be able to attribute fear to other people or animals, but we can.

Box 2. Conscious and unconscious fear

There is a large literature investigating the role of consciousness in fear, but it is heterogeneous in regard to the content of that conscious experience. Some studies have shown that stimuli that communicate or trigger fear can do so even when perception of those stimuli is subliminal, at least to some degree, a mechanism that appears to involve the amygdala (good evidence; [129, 130]). Others have claimed that such nonconscious fear processing depends on a particular subcortical route of input to the amygdala that typically bypasses cortex (debated; [75, 131, 132]).

More controversial is the possibility of unawareness of the feeling of fear itself, rather than just of the eliciting stimuli. However, non-conscious emotions have been proposed as a possibility based on some psychological experiments [133]. Regardless of the empirical status of these dissociations, they highlight the different components of an experience of fear: one can be aware of the eliciting stimuli and circumstances (often the object towards which the fear is directed behaviorally); one can be conscious of the bodily changes that accompany fear; one can be conscious of one's ability to act in response to and cope with the fear-eliciting situation; one can be conscious of one's change in cognition; and one can be conscious of many associated thoughts and background knowledge related to fear [14]. When people report that they feel afraid, they could be reporting on their awareness of any number of these components.

Box 3. Psychopathology of fear

Despite the high inter-individual variability in fear responses, there are consistent patterns across time within an individual. That is, many aspects of fear and anxiety can usefully be characterized as traits, in humans as well as other animals [82, 134]. As with moods in general, there is substantial heritability for trait anxiety, and for anxiety disorders, although it seems clear that most of the genetic variance is accounted for by complex polygenic interactions with environmental stressors, rather than by any single gene [135]. The decoupling between an immediate stimulus trigger and a fear state also makes trait anxiety prone to dysregulation: anxiety disorders constitute one of the most common psychiatric illnesses (all in all, close to 20% of the population suffers from an anxiety disorder of some kind in any given year [136]).

There are clinical distinctions between dysfunctions of fear processing that have some evidence for involvement of specific brain structures and neurotransmitter systems, making them candidates for functional subtypes of fear that will be reflected in the brain. Generalized anxiety disorder features chronic worry about a range of events, typically focused on the future. Panic disorder, on the other hand, results from a severe and acute fear response-- often in the absence of an ability to cope, such as the sensation of suffocation that can be experimentally induced by inhaling carbon dioxide (other experimental inducers of panic are intravenous administration of lactate or cholecystokinin). Phobias are characterized both by predictive anxiety as well as acute flight responses, often to specific classes of stimuli (e.g., spiders or snakes). Ever since Freud, anxiety disorders have been viewed as resulting from pathological suppression, repression or avoidance of fear-eliciting situations, thoughts, and stimuli [137]. The reasonable hypothesis based on such views is that treatment should emphasize exposure to fear-inducing stimuli, and access to fear-related thoughts and memories [138, 139], essentially updating emotional information [140]. The psychological concepts related to anxiety and its treatment have been mapped onto behavioral processes such as adaptation and extinction, and onto their neural correlates [141], a thriving corpus of research in modern neuroscience.

There are alternative possibilities for how pathology might emerge from fear, not mutually exclusive with the above: it simply might represent an exaggerated fear reaction. Phobias would be an example. One plausible point in processing for such exaggeration to exert its effect would be at the earliest stage (a component that itself may involve learning: discrimination among stimulus properties that evoke conditioned fear becomes broader after aversive learning [142]). Thus, increased expectation of, and rumination about fear, can be associated with increased vigilance and attention to potentially dangerous stimuli [143, 144]. The consequence is a generally heightened state of arousal, accompanied by many fear-like responses that can be thought of as false positives from a signal detection perspective. The threshold for detecting fear has simply been set too low and too many stimuli that have a very low probability of being dangerous are misinterpreted as dangerous [145]. One might wonder why pathological anxiety should be so prevalent at all. Is it so hard to set the right threshold? The solution is to realize the asymmetry between false negatives (which can result in death) and false positives (which, in isolation, often have few consequences). It is only when false positives cumulatively begin to impair daily functioning, or when their number increases as environmental circumstances change, that pathology becomes evident. An example illustrates the point [146]: You are a hunter-gatherer at a watering hole and hear a noise, which could be a lion. Suppose the cost of fleeing in panic is 200 calories, and the cost of engaging a lion is 200,000 calories. Some simple calculations show that you should flee

in panic if the probability of the noise being a lion is 1/1000 or greater. Which means that 999/1000 times you are panicking with no lion, i.e., you have a false positive.

There is yet another view regarding pathological states of fear: that they arise from the operation of a module that is relatively impenetrable to control, operates relatively automatically, and has been tuned by evolution. All these features could render such a module not only difficult to override, but also responsive to stimuli in a way that would have been adaptive in our ancestral environment but may no longer be so. This view is supported by responses to so-called “prepared stimuli”, objects such as snakes and spiders that are the most common targets of specific phobias and that can be more easily conditioned (or, indeed, need not be conditioned at all) to produce fear [83]. Another distinguishing feature of such fear modules typically is the proposal that they can operate, to some extent, outside conscious awareness of the eliciting stimuli (cf. Box 2).

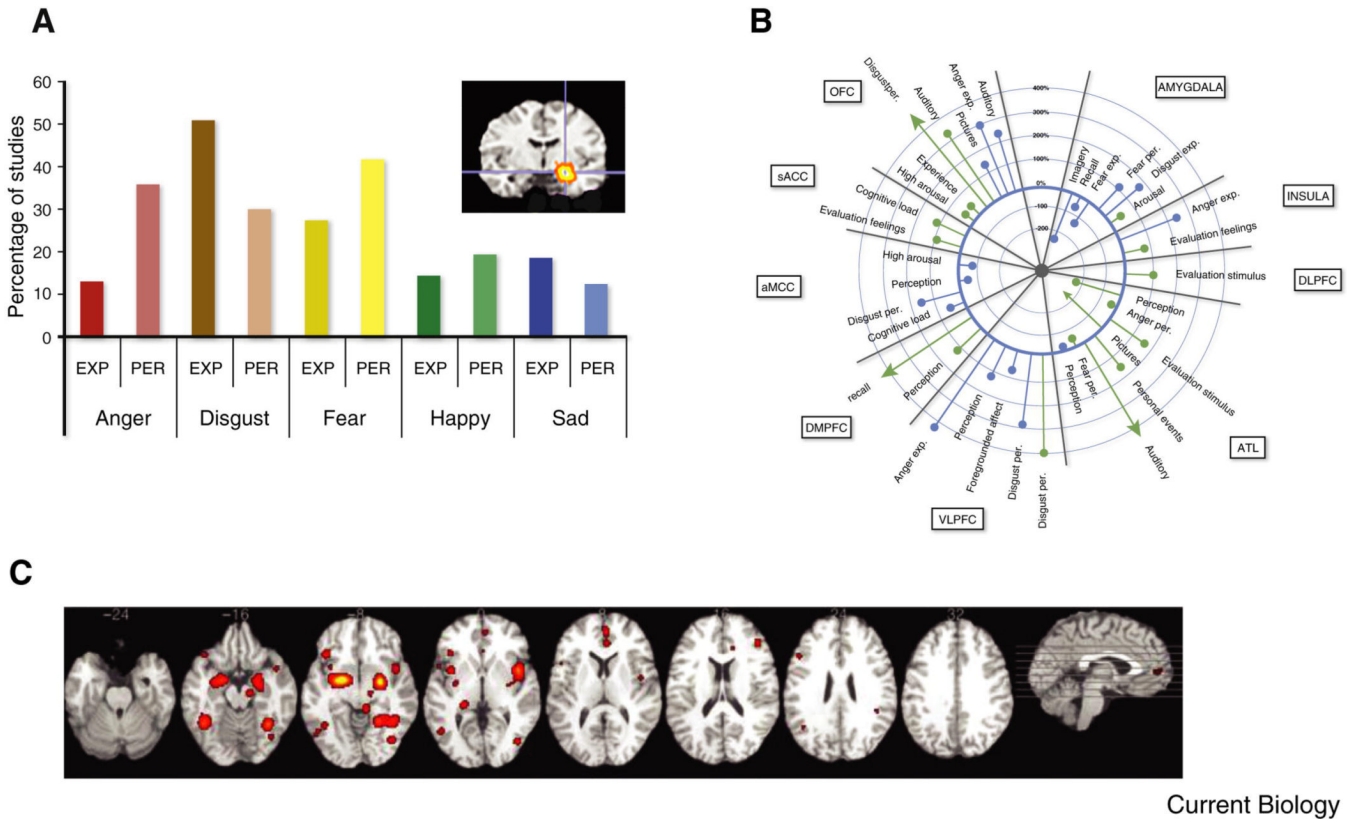

Figure 1. Neuroimaging of emotion in humans

(A,B) Examples suggesting that there is no focused neural network for fear, but that emotions are instead processed in a very distributed fashion. (A) Meta-analysis of activation in the amygdala. The y-axis plots the proportion of studies surveyed that showed significant activation within 10mm of the amygdala (inset), broken down in terms of studies looking at the perception (per) or experience (exp) of particular emotions. (B) Significant activations in specific brain regions (structures in boxes around the outside of the circle) as a function of specific processes (blue lines: left hemisphere, green lines: right hemisphere). The percentage plots from the origin denote the change in odds that an activation would be seen, from logistic regression of the meta-analysis. Modified from a meta-analysis of 91 neuroimaging studies [126]; see also [11]. Abbreviations: DLPFC=dorsolateral prefrontal cortex; ATL=anterior temporal lobe; VLPFC=ventrolateral prefrontal cortex; DMPFC=dorsomedial prefrontal cortex; aMCC=anterior middle cingulate cortex; sACC=subgenual anterior cingulate cortex; OFC=orbitofrontal cortex. (C) Example to the contrary, suggesting that there is a focused neural network for fear, prominently including the amygdala. Activation likelihood maps of fear are shown from another meta-analysis of 30 recent neuroimaging studies [8]; here hotter colors represent greater spatial overlap (consistency) among significant activations across multiple studies in the meta-analysis. The amygdala is prominently activated across studies of fear.

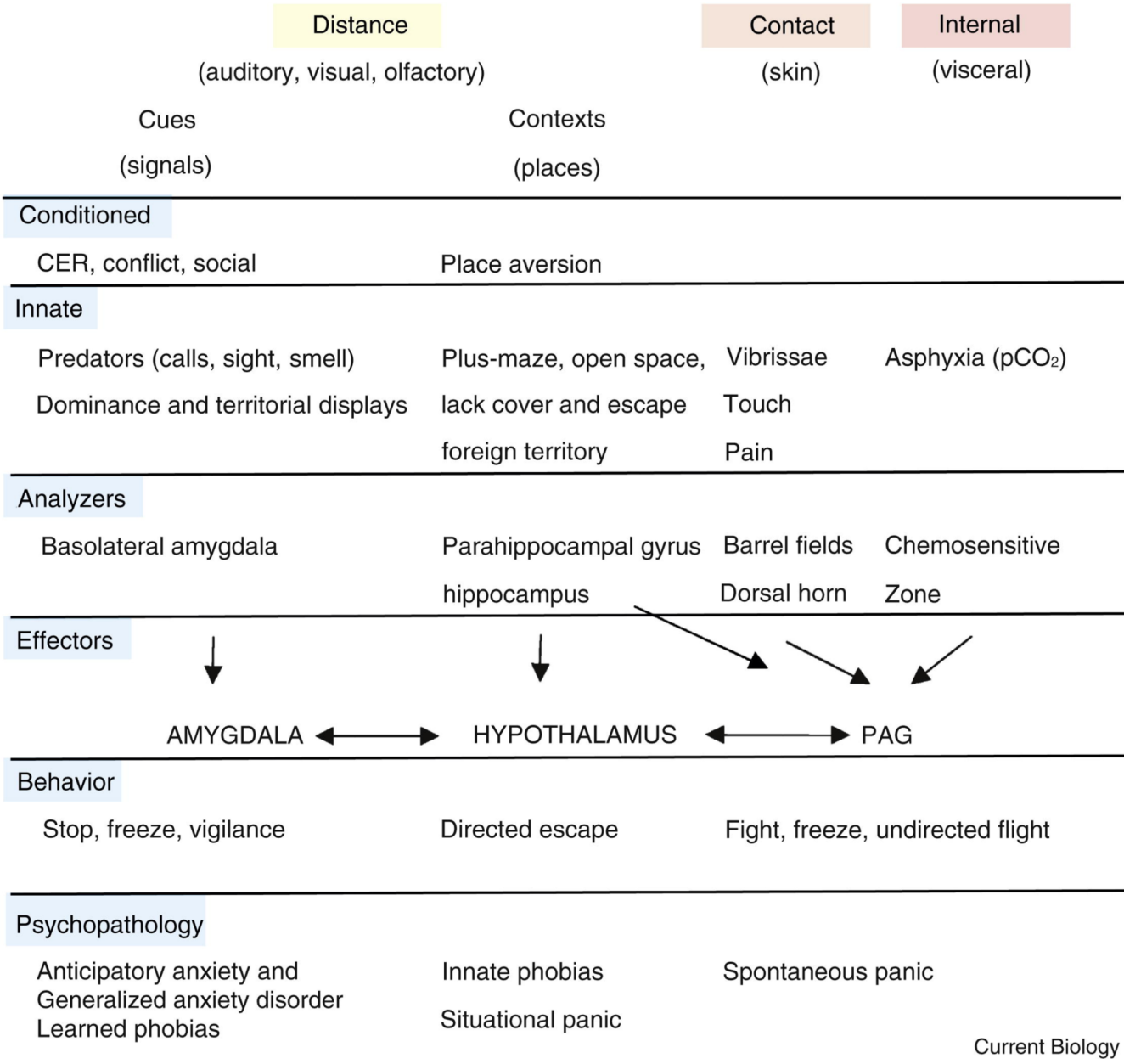

Figure 2. The amygdala

(A) Some of the main amygdala nuclei and their inputs and outputs, emphasizing the complex internal architecture of this structure. (B) Amygdala connectivity with other brain structures, emphasizing its participation in multiple networks that process fear, and its central location in mediating between parts of the prefrontal cortex and nuclei in the hypothalamus and brainstem. Modified from [69] and [120]. Abbreviations: MDm: dorsomedial thalamus, which mediates between amygdala and medial prefrontal cortex; Ca, Acc, P, VP: components of the basal ganglia (Caudate, Accumbens, Putamen, Ventral Pallidum); Ce, AB, B, L: nuclei of the amygdala (Central, Accessory Basal, Basal, Lateral); EC: entorhinal cortex.

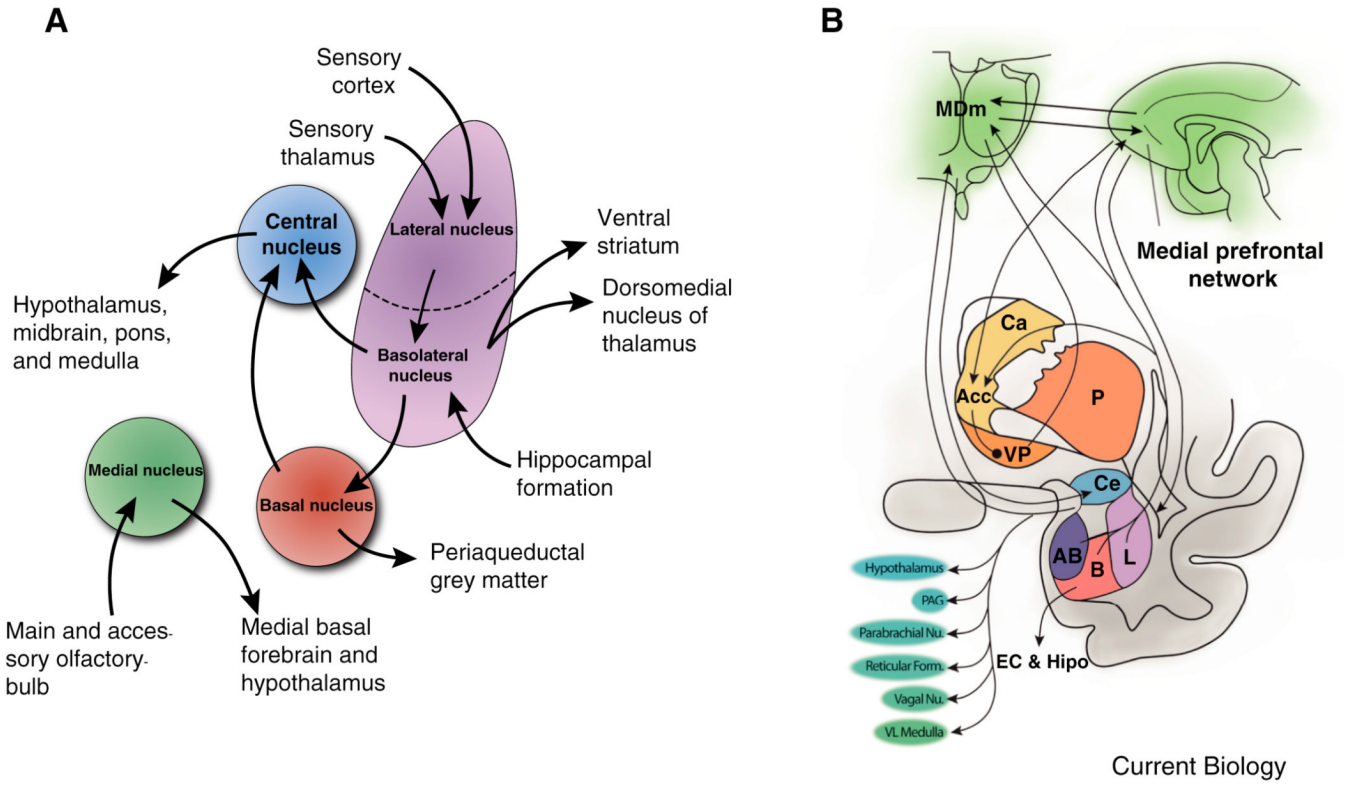

Figure 3. Functional components of fear: stimuli, cognition, and behavior

(A) Stimuli and behaviors related to fear, schematized in terms of their complexity and the degree of an organism's involvement and control (regulation). Fear can be caused by a wide range of stimuli, from basic unconditioned stimuli to complex symbolic knowledge; and it can in turn trigger core biological responses as well as be modulated volitionally, at least in humans. Very roughly, the components at the upper left are shared across a wider range of species, whereas the components at the bottom right may be unique to humans. (B) Schematic of some of the effects of a central state of fear on cognition and processing mode. Fear interfaces with nearly all other aspects of cognition.

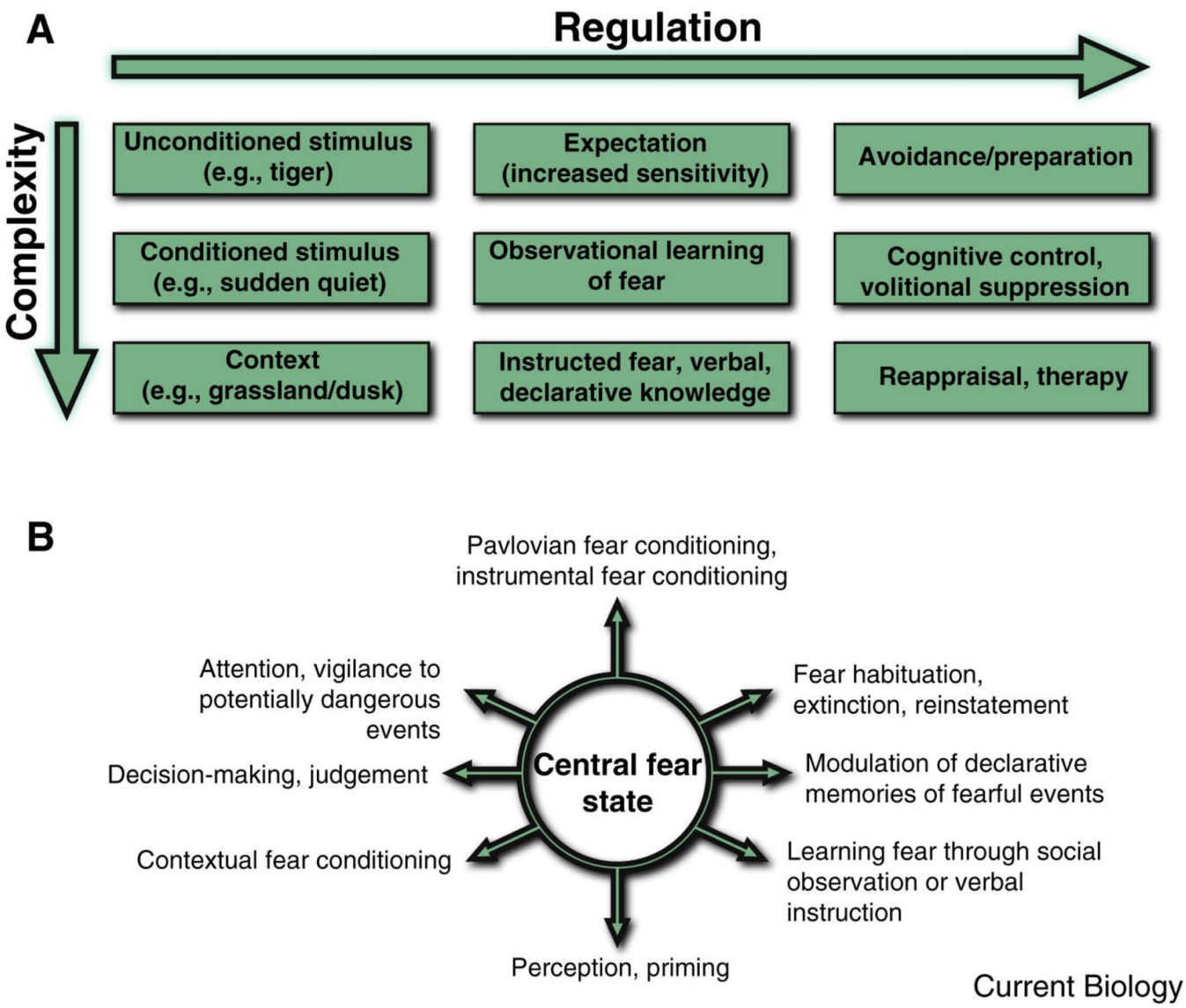

Figure 4. Fear, the amygdala, and distance

Physical distance (proximity) is one of the most basic stimulus cues to trigger fear. (A) Different adaptive types of fear behaviors can be elicited as a function of distance, ranging from freezing to fleeing to defensive attack. Adapted from [74], see also [20] for a similar scheme. (B) Lesions of the human amygdala reduce interpersonal distance and the sense of invasion of personal space. At the top are schematized the mean interpersonal distances from an experimenter for healthy controls (left) and a patient with bilateral amygdala lesions (patient SM, right). At the bottom is a plot of the data showing mean distance that people felt comfortable standing from the experimenter (at the origin), patient SM is the red bar and the rest are healthy controls. From [91]. (C) Approach or retreat of a threatening stimulus (a tarantula) in a human fMRI study showed differential activation of the amygdala and bed nucleus of the striaterminalis. Participants lay inside the fMRI scanner while their foot was placed in compartments at varying distances from the tarantula, a procedure they observed through video (left panel). Subtraction of approach minus retreat (for the same distance, middle panel) resulted in the activation shown on the right panel. From [96].

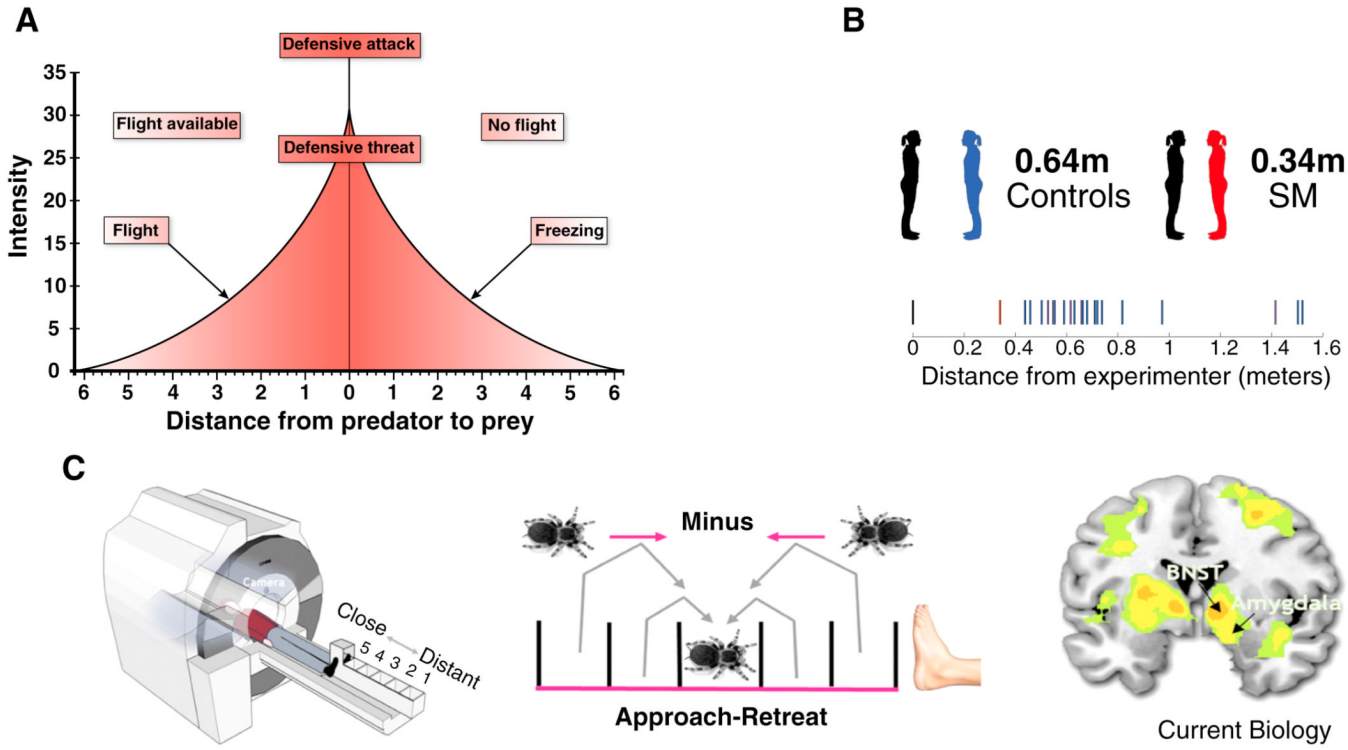

Figure 5. Components of a central fear system

The schematic outlines some of the processing that contributes to fear, including sensory inputs, central structures, and effectors. From [31].

Table 1

Emotion theories of fear.

Type of Theory	Key Features	Reference
Motivation/Personality	5 types of fear: evolutionary danger, novelty, intensity, learning, social	[82]
Neurofunctional	2 systems: fear and panic	[12]
Adaptive/Evolutionary	Fear is an instance of a more basic and broader survival system	[13]
Basic Emotion	Fear is one of a small set of basic emotions, which are cross-cultural	[3, 147]
Modular	Phobias (to snakes, spiders, etc.) reflect the operation of modules	[83]
Modular	Pain, predators, and conspecific aggression are 3 types of fear	[21]
Dimensional	Fear is one location in a 2-D space of arousal and valence (“core affect”)	[4]
Dimensional	Fear is one location in a 2-D space of reward and punishment	[15]
Social Construct	The experience of fear in humans is constructed from core affect	[14]

A sampling of some of the commonly encountered frameworks for thinking about fear. For a more general introduction to psychological theories of emotion, see [127, 128].

Table 2

Measures of fear in rodents (top) and humans (bottom).

Behavioral Test	Measure of Anxiety
open field exploration	isolated animal avoids bright open areas and prefers secure nest
elevated plus-maze	isolated animal avoids open arms of an elevated maze and prefers closed arms
social interaction test	animal in a male pair reduces interaction time with the other animal
hypophagia	reduced food intake when anxious (e.g., in novel environments)
burying behavior	increased burying of food or other objects
open field emergence	less emergence into an open space from a secure nest
enhanced startle	increased startle to a loud noise, to conditioned or unconditioned fear stimuli

Psychophysiology/ endocrine	Fear Questionnaires
Skin-conductance response (autonomic arousal)	State-Trait Anxiety Inventory
Potentiation of auditory startle (measures several emotions)	Beck Anxiety Inventory
Facial EMG (measures several emotions)	Fear Survey Schedule
Heart rate, respiration (measures several emotions, not specific)	Fear of Negative Evaluation Scale
Pupillometry (autonomic arousal)	Social Avoidance/Distress Scale
Salivary cortisol (long-duration arousal, stress)	Anxiety Sensitivity Index
	Albany Panic and Phobia Q.
	Fear Questionnaire
	PANAS-X Fear

The table is only a partial listing of the many behavioral measures that can be used to index fear and anxiety. Whereas the rodent tests are all behavioral, probes in humans encompass a smaller set of psychophysiological measures and a large set of self-report questionnaires (see [39] for details on these).

Table 3

Correlations between prototypical fear scenarios (left column) and ratings of behavioral response in humans.

	Attack	Run	Freeze	Risk assess	Scream	Hide
Dangerousness	0.35	0.56	0.05	−0.90	0.56	−0.15
Inescapability	0.65	0.05	0.49	−0.51	0.74	−0.35
Distance (far)	−0.64	0.31	−0.71	−0.13	−0.32	0.63
Identifiability (not ambiguous)	0.29	0.63	0.06	−0.86	0.39	−0.21
Place of concealment	−0.71	−0.17	−0.28	−0.42	−0.39	0.63

The left column lists attributes on which verbal scenarios were rated; these were derived from ecological studies of rodents. The columns to the right list correlations with the types of responses given by 79 women in the study [2].